As a preliminary matter, applicants address the objection to the Specification made by the Examiner regarding the content of original pages 13, 20 and 28. While the grounds and authority for such objection are unstated, applicants have acquiesced to the Examiner's position and deleted the content of original pages 13, 20 and 28 respectively. In addition, applicants have amended the Specification text at page 7, line 19 to include brief figure descriptions for newly added figs. 8. 9 and 10 respectively, each of which present again the entire content of original Flow Scheme A, Table 3, and Table 4 as such.

Applicants respectfully question the Examiner's requirement for such strict formality as well as the objectivity of the Examiner's standard for deciding what constitutes proper subject matter for inclusion as a table within the Specification rather than what must be presented as a figure in the Drawing as such. Nevertheless, to avoid senseless argument, applicants have added new Figs. 8, 9 and 10 respectively and acceded to the Examiner's explicit demands on this issue. For these reasons, applicants therefore request that the Examiner reconsider her stated position and withdraw this ground of objection against the Specification.

Applicants will now address each substantive basis for rejection stated by the Examiner in the instant Official Action with respect both to the legal requirements and the relevant factual circumstances. Because so much of the Examiner's stated views and positions are dependent upon having a clear understanding of applicants' invention as defined by the language of the now pending claims, applicants deem it both useful and necessary to summarily review the subject matter as a whole which is applicants' claimed invention.

I. Applicants' Invention as Claimed.

Applicants' invention is defined in the alternative by amended claims 1-10 and by claims 11-14. Claims 1-10 define a method while claims 11-14 are composition of matter definitions directed to a family of pharmacologically active compounds for use in the recited methodology.

It will be recognized and appreciated that amended independent claim 1 is directed to a method for stimulating angiogenesis within a targeted collection of viable cells in-situ; whereas amended independent claim 2 defines a method for altering proteasome-mediated degradation of peptides in-situ within a collection of viable cells. As amended, each of independent method claims 1 and 2 are mirror images of the other in their requirements and in their manipulative steps. Each method claims identifies a collection of cells in-situ as the target; provides means for introducing at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of the targeted cells; introduces at least one member of the PR-39 oligopeptide collective to the targeted cells; and then explicitly requires that the introduced PR-39 oligopeptide collective member interact with such proteasomes as are present within the cytoplasm of the targeted cells such that three specifically stated events must occur. These are: that the proteasomes interact either directly or indirectly with the introduced PR-39 oligopeptide collective member; that the proteolytic degradation mediated by these proteasomes against an identifiable peptide becomes markedly altered while the proteolytic degradation against other individual peptides remains unaltered; and that the markedly altered proteolytic degradation of these proteasomes results in a stimulation of angiogenesis in-situ (as recited by claim 1) or results in an increased expression of an identifiable peptide such as IKβα or HIF- 1α (as recited by claim 2).

It will be appreciated also that applicants' invention as defined by amended claims 1-10 individually is presented in the form of a method or process having a series of explicitly stated manipulative steps. As codifies in 35 U.S.C. 100(b), method claims may include a new use of a known process, machine, manufacture, composition of matter or material; and this form of claiming also applies to a newly recognized use for a composition of matter regardless of whether the material is a previously known composition or an entirely novel composition. Accordingly, the essential questions for the Examiner for purposes of 35 U.S.C. 102 and 103 is whether the claimed method – defined as a series of manipulative steps – is a process which is novel and non-obvious to a person of ordinary skill in the field of the invention.

Equally important, when evaluating the novelty and patentability of applicants' defined method claims 1 and 2 respectively, it is not pertinent whether the employed compositions of matter (the PR-39 oligopeptide collective) are themselves known, or are new, or are themselves unobvious. The true issue is, rather, whether the recited steps defined by the method claims would have been known or obvious in light of the teachings in the prior art references given the perspective of the ordinary practitioner in that field [In re May, 197 U.S.P.Q. 601 (C.C.P.A. 1978)].

Also it will be recognized that each of the dependent claims 3-10 respectively depend from amended independent claims 1 or 2 individually. Accordingly, the subject matter as a whole is most broadly defined by amended independent claims 1-2 individually and by claims 1-10 collectively. Applicants therefore request that the Examiner carefully consider the language presented by the recited steps of amended independent claims 1 and 2 now pending in the present application.

Finally, pending claims 11-14 are composition of matter claims which define a novel family of PR-39 derived oligopeptides whose members are pharmacologically active and individually can cause a marked alteration of proteasome-mediated degradation for at least one individual peptide in-situ after being introduced to a viable cell. Amended independent claim 11 recites five specific requirements for each member constituting this family of derived oligopeptides. These requirements include: the maximum length of each oligopeptide is less than 26 amino acid residues in length; each oligopeptide begins with the sequence Arg-Arg-Arg at the N-terminal end; each oligopeptide is devoid of the amino acid sequences "Pro-Pro-X-X-Pro-Pro-X-X-Pro" and "Pro-Pro-X-X-X-Pro-Pro-X-X-Pro" where X is any amino acid; each oligopeptide is able to interact in-situ with such proteasomes as are present within the cytoplasm of the cell; and each oligopeptide is able to alter markedly the proteolytic degradation activity of these proteasomes such that a marked increase expression of an identifiable peptide occurs as a consequence.

In addition, the Examiner will recognize that all the members of this oligopeptide family are required to demonstrate these attributes. Exemplifying merely three of the preferred members of this oligopeptide family are those amino acids residue sequences defined by dependent claims 12, 13, and 14 respectively. It will be noted and appreciated that these dependent claims define family members having 15, 11, and 8 amino acid residue lengths; and in that the amino acid sequence for each of these residue lengths complies fully with the requirements recited by independent claim 11.

II. The Antecedent Descriptive Basis Supporting The Amended Claim Language

Applicants respectfully direct the Examiner's attention to Specification text in order to demonstrate the presence of an ample and complete description for each and every manipulative step of the methodology defined by amended independent claim 1 and 2 respectively herein. The underline mechanisms for the methodology is described beginning at page 9, line 16, and continues through page 11, line 20. As repeatedly disclosed therein, one essential requirement is the presence of a proteasome and at least one member of the collective of PR-39 oligopeptides. Also, the detailed description for the alternative mechanisms of interaction for proteasomes and selective polypeptide degradation function is described in detail particularly beginning at page 10, line 5 and continuing through page 11, line 8.

In addition, the membership of the PR-39 oligopeptide collective is also described in precise, clear, and explicitly complete detail within the Specification beginning at page 23, line 4 and continues through page 27, line 7. Attention is directed to the Specification text at page 24, lines 15-23 in particular – especially with regard to the information presented at page 26.

III. The Rejection of the Claims Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected original claims 1-10 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The problem appears to be centered on the use of the word "selectively" and the term "selectively inhibited" within the original claim language.

As stated, the Examiner has specifically focused her remarks [page 3, middle of the instant Official Action] on the word "selectively" and the meaning of this word within the manipulative steps recited by the originally submitted claims. Applicants respectfully submit that the Examiner is indulging in semantic gamesmanship. It is clear from the description provided by the Specification text itself that the term "selectively" refers to and defines the empirically demonstrated fact that, upon binding to any member of the PR-39 oligopeptide collective, the proteolytic degradation capacity of the proteasomes becomes markedly altered such that specific degradation of individual peptides such as HIF- 1α and IKβα is reduced – but without altering the proteolytic degradation of other individual peptides such as p105 and p50. NFKB. Thus, the plain meaning of the word "selectively" is fully disclosed and described in detail in the Specification.

Consequently, with respect to the Examiner's stated view and position on this issue, applicants respectfully submit that there is no information or descriptive content which is lacking from the written disclosure of the Specification text which could meaningfully effect or influence the meaning of the term "selectively". Yet, the Examiner has chosen to question this language and has rejected the original claims as being vague because of the term "selectively".

The sole rationale explanation for the Examiner's stance, in so far as applicants can understand, is a subjective reluctance and personal opposition to the word "selectively" as employed within the language of the original claims defining the methodology. The doctrine of "In hac verbis" has long been formally disavowed and abandoned by the U.S. Patent Office; and, a part of this reform and revised patent policy, is the now well-established practice to avoid any requirement or need to present formal language definitions and

recitations of word meanings – especially when the disclosure of the Specification text makes the proper meaning and operational definition of the word or phrase clear and functionally understood in context.

Applicants have neither need nor desire to argue semantics or personal quirks with the Examiner. It is, however, applicants' purpose and intent to advance the prosecution of this application on substantive grounds.

Thus, solely in order to resolve such questions in an expeditious manner, applicants have chosen to amend the language of the methods defined by independent claims 1 and 2 by deleting the term "selectively" and substituting instead a recitation of what this term encompasses. In this manner, the Examiner's stated view and position has been effectively met and satisfied; yet, the true meaning presented within the Specification text and recited within the manipulative steps of the method is explicitly set forth with particularity and precision.

Similarly, the specific wording of dependent claims 9 and 10 respectively have been amended to delete the term "selectively". Such limited amendment is believed to be proper and correct in all aspects.

Overall therefore, applicants have substantively amended claims 1-2, 5-6 and 9-10. The alleged flaws in wording identified by the Examiner have been addressed in these claims; and the original claim language has been amended to meet the Examiner's stated basis for rejection as well as to define precisely the subject matter as a whole which is the applicants' methodology. The amended language of all these claims is therefore believed to be correct and satisfactory in all respects with regard to the requirements of the second paragraph of 35 U.S.C. 112.

Finally, as regards the language of the pending claims as a whole, the first inquiry is to determine whether the claims do, in fact, set out and circumscribe a particular area or subject matter with a reasonable degree of precision and particularity. It is here where the meaning of the language employed to define the invention is analyzed; not in a vacuum, but always with regard to the teachings of the prior art and within the particular use or application disclosed by the Specification as it is understood and interpreted by one possessing ordinary skill in the pertinent art [In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976)]. Applicants note that each of the terms used in pending claims 1-14 is well understood; is not subject to numerous definitions and interpretations; and that there is no discrepancy, no confusion, and no ambiguity with regard to the antecedent descriptive basis provided by the Specification text. Rather, the language of the claims as a whole now pending read on subject matter which is completely disclosed and enabled by the Specification text. Moreover, each of the pending claims is explicit and clearly stated; and sets forth and circumscribes the particular subject matter area with the requisite reasonable degree of precision and particularity [In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971)].

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the requirements of precision, clarity, and particularity required by the second paragraph of 35 U.S.C. 112. Accordingly, applicants respectfully request that the Examiner reconsider her stated position and withdraw this ground of rejection against the presently pending claims.

IV. The Rejections Under 35 U.S.C. 102(b) and 103(a)

The Examiner has rejected original claims 1-10 under 35 U.S.C. 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being obvious over the Gallo et al. reference, U.S. Patent No. 5, 654, 273. The rationale of the Examiner explicitly states that the '273 patent reference discloses a 'method for treating angiogenesis using PR-39 is known in the art'; and also explicitly states that because the original claims in the present application are drawn to a method of using a known peptide for treating a condition taught by the art – regardless of the mechanism of action employed – applicants' original claims are deemed to be 'inherently anticipated' and/or 'rendered obvious by the art'.

Applicants respectfully point out and affirm that the Examiner is factually incorrect and legally in error as regards the issues of novelty and non-obviousness. The Examiner has apparently failed to note or appreciate that the cited and applied Gallo et al. patent reference is not directed to means or methods for stimulating angiogenesis, but instead is directed to inducing syndecan –1 and –4 expression in mesenchymal cells; and that the disclosure requires that the necessary number of amino acid residues in the peptide residue sequence (and any of its modified forms) include the presence of all 39 amino acid residues in order that the peptide show any biochemical activity. This absolute requirement of at least 39 amino acid residues for biochemical activity is openly stated and described in the patent text [Column 3, lines 16-45].

Also, the Examiner has acknowledged that the single cited and applied reference (the '273 patent), does not explicitly or directly disclose those particular attributes, properties and capabilities of the method defined by original claims 1-14. Instead, the entirety of the Examiner's reasoning is based on inherency. The Examiner's remarks and conclusions (as stated at pages 4-5) also state that the mechanism of action recited by the original claims

under review is not relevant or material to the issues; and that all the peptides described in the '273 patent inherently possess the characteristics recited in the instant claims (and therefore anticipate the method comprising applicants' invention) or make the method of applicants' invention merely an expected and obvious modification of what is actually disclosed by the cited and applied patent reference.

Clearly, the entire substance of the Examiner's presentation, rationale, and position is centered on the legal doctrine of inherency as it applies to this single prior art reference. Accordingly, a summary review and proper understanding of the legal doctrine of "inherency" is in order.

The legal doctrine of "inherency" holds that anticipation (and also in this instance obviousness) may be established when one (or a combination of prior art references) either discloses exactly or suggests overtly a claimed invention; and also is established when the natural and invariable practice of the references' disclosure would necessarily and reasonably intrinsically meet all the elements of the invention as presently claimed.

Unfortunately, the Examiner has failed to recall that the legal doctrine of inherency is available only when the claimed invention can be identified or inferred from the disclosure within the prior art reference with substantial certainty. Probabilities and speculation are not a substitute for substantial certainty; and probabilities and speculation are not legally sufficient to invoke and apply the inherency doctrine [In re Oelrich, 212 U.S.P.Q. 323 (C.C.P.A. 1981); In re Chandler, 117 U.S.P.Q. 361 (C.C.P.A. 1985)].

In order for a claimed invention to be inherently disclosed, the defined invention claimed in the pending patent application must be necessary and only reasonable construction to be given to the prior art disclosures; and the resultant claim must inevitably occur and be

the result of what is revealed in the prior art. Moreover, the mere fact that a certain thing may or might possibly result from the set of factual circumstances is not legally sufficient to establish inherency [In re Robertson, 49 U.S.P.Q. 2d 1949 (Fed. Cir. 1999)]. The legal burden thus lies upon the Examiner to demonstrate that any of the cited and applied prior art references provide the desired result, consequence, property, or trait with substantial certainty. If, however, the consequence, property, or result could only potentially or speculatively occur as a theoretical possibility or contingent event within the factual setting, then this basis is inadequate legally and insufficient [Continental Can Co. U.S.A. Inc. v. Monsanta Co., 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991)].

It is therefore well established, as a matter of law, that for an attribute or result to be deemed as inherently disclosed or suggested, it is not sufficient that the ordinary person following the prior art disclosure(s) might obtain the result set forth. To the contrary, it is legally demanded that the attribute or result must invariably happen. Inherency as a doctrine and legal basis cannot be established upon a speculation or where reasonable doubt as to the occurrence of the inevitable result exists [In re Wertheim, 191 U.S.P.Q. 90 (C.C.P.A. 1976)].

In addition, the factual basis presented by the '273 patent, which the Examiner believes to offer support for inherency rejection, must be read and understood as written. Attention is thus directed to column 3, lines 16-60 in particular as exemplifying what the Examiner has employed wrongly and subjectively as the alleged factual basis. This detailed disclosure states the following points of information: (1) The PR-39 amino acid sequence must be employed at a minimum as a 39 amino acid residue sequence in order for biological activity to be demonstrated. (2) The entire 39 amino acid sequence of PR-39 can be part of a larger sized molecule such as a fusion protein, or when a mobilized to an inert substrate or

targeted using a specific ligand, as part of a longer length protein. (3) The entire PR-39 peptide (and any of its longer length products) are collectively identified as "synducins" – all of which are characterized by a specific biological activity and mechanism of action described in the examples within columns 6-10 respectively. (4) The "synducin" characteristics and limited mechanism of action are the specific inducement of syndecan-1 and syndecan-4 expression on the surface of mesenchymal cells. This is achieved via specific inducement of syndecan-1 and syndecan-4 mRNA within cells; or by an increase in the level of cell surface heparan sulfate and rapid up take of such heparan sulfate into mesenchymal cells to a saturation level. (5) The biochemically active PR-39 compositions must include a specific and lengthy amino acid sequence which is: PRO-PRO-X-X-PRO-PRO-X-X-PRO and PRO-PRO-X-X-X-PRO-PRO-X-X-PRO, where X is any amino acid.

These are explicit, direct, and unrelenting requirements for the Gallo et al. peptide sequences and the limited utility and function recognized for these compounds. Thus, the Examiner has failed to recognize that there is no information and no factual suggestion whatsoever for using these peptides other than for the specific inducement of syndecan-1 and syndecan-4 expression on the surface of mesenchymal cells. The entire mechanism of action described and the steps of the disclosed methodology is specified and compulsory for syndecan expression alone as stated by the limits of description within this reference.

Moreover, the entire metrology of use for any and all purposes is stated explicitly at column 5, lines 1-60 of the '273 patent; this disclosure demands that the inducement of syndecans on the cell surface be a requisite part of each and every usage, clinically or otherwise. Thus, any series of manipulative steps which employs and relies on the information disclosed by this '273 patent reference must incorporate all these severe

restrictions as stated explicitly by this reference in order for any utility or clinical result to be expected or foreseen.

Equally important are the limits of the method and compositions explicitly disclosed by this '273 patent, as demonstrated by Example 4 [disclosed at column 8, lines 51-65]. It is noted that the use of these peptides failed to perform or be active in a variety of non-mesenchymal cells as tested; and showed that if the targeted cells were not mesenchymal cells as such, no functional response or biochemical activity was demonstrated or could be expected [Column 8, lines 60-65]. In sum, all the information disclosed or suggested by the '273 Gallo et al. patent is self-limiting, self-contained and extraordinarily restrictive in its requirements and uses.

Applicants therefore respectfully submit and affirm that the Examiner's position and presumption as stated is a fallacy and the Examiner's reliance upon inherency is based solely upon an unproven and speculative theory which has no factual basis to support it. Applicants also respectfully maintain that the Examiner has not presented or established any evidence with the requisite degree of substantial certainty which proves any inherent property with regard to angiogenesis capabilities or the discriminating inhibitory properties of the methods now recited by amended independent claims 1-10 herein. The Examiner's reliance and use of the inherency doctrine fails blatantly and may not be properly employed as a legal basis for rejection because the entirety of the evidence employed by the Examiner as the underline basis for rejection is purely speculative, and can at best be characterized as a theory without any realistic probability as such. This is demonstrated factually by the complete absence of relevant supporting information, knowledge, or data within the '273 patent – a publication

which is devoid of any direct or explicit mention of proteasomes, proteasome interactions or any changes in peptide degradation capabilities.

The Examiner has also utilized this '273 patent reference with regard to the composition claims recited by pending claims 11-14 herein. Applicants note that this prior art reference teaches away from the very characteristics, properties, and utilities demonstrated by applicants' defined invention. Applicants note in particular that the peptide compositions defined by presently pending claims 11-14 are all far shorter in length than the minimum 39 amino acid residue compositions of the '273 patent; are not part of a fusion peptide or linked with any other molecule; and do not comprise or contain the requisite amino acid sequences which are explicitly required by the disclosure of the '273 patent reference. Thus, the Examiner has no basis at all for suggesting or believing that any shorter length peptide sequence – particularly those of 15, or 11, or 8 residue length – could or would be biologically active or functionally useful for any purpose.

Applicants therefore affirm and maintain that the '273 patent reference of record does not teach and could not suggest to those of ordinary skill in the art that they should carry out the claimed process defined by claims 1-10 or employ the oligopeptide compositions defined by claims 11-14. Moreover, the single reference of record has also revealed that, even if the ordinary practitioner had thought of making or practicing applicants' claimed invention, those of ordinary skill in this field would not have any reasonable expectation of success. Applicants further maintain and submit that there is nothing inherent or intrinsic in the cited and applied prior art of record which provides a basis for any expectation which would render the subject matter of independent claims 1-14 respectively as being either implied or obvious. Accordingly the subject matter as a whole defined by claims 1-14 is a

methodology and family of compositions which are novel and have substantial patentable merit.

In addition, applicants have recently found another publication which further demonstrates and reinforces the limited expectations for the PR-39 peptide as a biochemically active composition. This publication is U.S. Patent No. 5, 830, 933. The Examiner's attention is directed to the explicitly stated information in this publication that only the 39 and 26 amino acid residue length peptides were found to show any biological activity; all the peptides tested having a size less than 26 amino acid residues in length were empirically shown to be biologically inactive A copy of this '933 patent is enclosed for the Examiner's information and review.

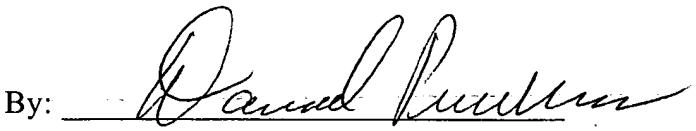
For all reasons stated herein, applicants respectfully submit that multiple errors of fact and law have been made by the Examiner; and that, accordingly, independent claims 1, 2 and 11 are therefore allowable as presently defined.

Claims 3-10 and 12-13 depend from independent claims 1-2 or 11; and merely provide particular limitations and preferred embodiments to the unique and non-obvious invention defined therein. Since independent claims 1-2 and 11 are believed to be in condition for allowance and claims 3-10 and 12-13 respectively depend there from, these dependent claims are also believed to be allowable.

In view of the above discussion and detailed analysis of the many factual and legal errors presented by the Examiner, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiner is invited to call applicants' undersigned attorney should she feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted.

MICHAEL SIMONS
YOUHE GAO

By: 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Michael Simons & Youhe Gao
SERIAL NO.	:	09/426, 011
FILED	:	October 25, 1999
FOR		"METHOD FOR PR-39 PEPTIDE REGULATED STIMULATION OF ANGIOGENESIS"
EXAMINER	:	F.T. Moezie
GROUP ART UNIT	:	1653
ATTORNEY'S DOCKET NO.	:	B75-043/CIP

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commission for Patents, Washington, D.C. 20231 on: June 18, 2001.

Attorney for applicants: David Prashker

Signature: David Prashker

Date: June 18, 2001

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MARKED UP VERSION OF AMENDED CLAIMS SUBMITTED PURSUANT TO 37 C.F.R.1.121

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant, in fulfillment of and in accordance with the requirements of 37 C.R.F. 121 (b) (iii), hereby submits a marked up version of once-amended claims 1-2, 5-6, and 9-11 as follows:

1 (Once Amended). A method for stimulating angiogenesis within a targeted collection of viable cells in-situ, said method comprising the steps of:

identifying a collection of cells comprising viable cells in-situ as a target for stimulation of angiogenesis;

providing means for effecting an introduction of at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells;

introducing at least one member of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells using said effecting means;

allowing said introduced PR-39 oligopeptide collective member to interact with such proteasomes as are present within the cytoplasm of said targeted collection of cells whereby

(a) [at least] some of the proteasomes can interact directly with said PR-39 oligopeptide collective member while other proteasomes can interact indirectly with said PR-39 oligopeptide collective member, and

(b) [at least a part of] the proteolytic [activity] degradation of at least on identifiable peptide mediated by said interacting proteasomes becomes [selectively] altered while the proteolytic degradation mediated by said interacting proteasomes against other individual peptides remains unaltered, and

(c) the [selectively] altered proteolytic degradation [activity] of said interacting proteasomes results in a stimulation of angiogenesis in-situ within the targeted collection of viable cells.

2 (Once Amended). A method for altering [selective inhibition of] proteasome-mediated degradation of peptides in-situ within a collection of viable cells, said method comprising the steps of:

identifying a collection of cells comprising viable cells in-situ as a target;

providing means for effecting an introduction of at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells;

introducing at least one member of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells using effecting means;

allowing said introduced PR-39 oligopeptide collective member to interact with such proteasomes as are present within the cytoplasm of said targeted collection of cells whereby

(a) [at least] some of the proteasomes can interact directly with the PR-39 oligopeptide collective member while other proteasomes can interact indirectly with said PR-39 oligopeptide collective member, and

(b) [at least a part of] the proteolytic [activity] degradation of at least one identifiable peptide mediated by said interacting proteasomes becomes markedly altered while the proteolytic degradation mediated by said interacting proteasomes against other individual peptides remains unaltered, and

(c) the markedly altered proteolytic degradation [activity] of said interacting proteasomes results in an increased expression [a selective inhibition of proteasome-mediated degradation] of said identifiable peptide [peptides] in-situ within the targeted collection of cells.

5 (Once Amended). The method as recited in claim 1 or 2 wherein the means for an introduction of a PR-39 oligopeptide collective member include one selected from the group consisting of catheter-based [introduction] means, injection-based [introduction] means, infusion-based [introduction] means, localized intravascular [introduction] means, liposome-based [introduction] means, receptor-specific peptide [introduction] means, and slow releasing means for peptide secretion in living cells and sequested organisms.

6 (Once Amended). The method as recited in claim 1 or 2 wherein the means for an introduction of a PR-39 oligopeptide collective member includes [the] DNA sequences coding for at least one PR-39 oligopeptide collective member in an expression [PR-39 oligopeptides of different sizes inserted in a suitable] vector for transfection and subsequent expression of the PR-39 oligopeptide collective member [peptides] within said cells.

9 (Once Amended). The method as recited in claim 1 or 2 wherein degradation of 1K$\beta\alpha$ is [selectively] inhibited.

10 (Once Amended). The method as recited in claim 1 or 2 wherein degradation of HIF- 1α is [selectively] inhibited.

11 (Once Amended). A family of PR-39 derived oligopeptides whose members individually cause an alteration in [a selective inhibition of] proteasome-mediated degradation of at least one identifiable peptide [peptides] in-situ after introduction intracellularly to a viable cell, each member of said PR-39 derived oligopeptide family [being:]

being a peptide less than 26 [39] amino acid residues in length;

having a [at least partially homologous with the] N-terminal amino acid residue sequence which begins with Arg-Arg-Arg [of the native PR-39 peptide];

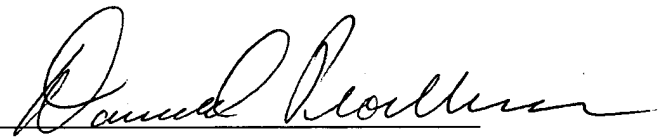
is a peptide devoid of the amino acid residue sequences Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro where X is any amino acid;

is able to interact in-situ with such proteasomes as are present within the cytoplasm of the cell; and

is able to alter markedly the proteolytic degradation of at least one identifiable peptide mediated by [activity of] said interacting proteasomes such that an [a selective] increased expression of said identifiable peptide [specific peptides] occurs in-situ.

Respectfully submitted.

MICHAEL SIMONS
YOUHE GAO

By: 

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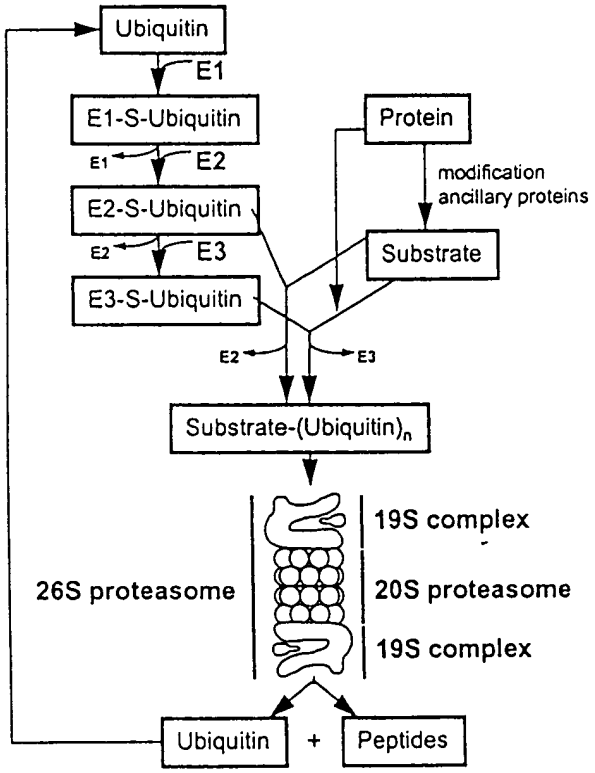
Flow Scheme A



*

Schematic representation of the proteasome-ubiquitin pathway. Ubiquitin is first activated by a ubiquitin-activating enzyme (UBA or E1) and passed on to a ubiquitin-conjugating protein (UBC or E2). Ubiquitin is then linked directly, or with the help of ubiquitin ligases (E3), via an isopeptide bond to a lysine residue of the substrate protein. Polyubiquitinated proteins are recognized and selectively degraded by the 26S proteasome, yielding reusable ubiquitin molecules and peptides of 5 to 15 amino acids. Conversion of a protein into a substrate for ubiquitination can in certain cases occur after posttranslational modification or association with ancillary factors. Proteins can also be recognized by an E3 ubiquitin ligase without prior modification or association

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* Reproduced from Gerards et al., CMLS 54: 253-262 (1998)

Fig. 8

Table 3: Schematic representation of the human 20S proteasome*

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* Reproduced from Gerards et al., CMLS 54: 253-262 (1998)

Fig. 9

Table 4:

(1) GENERAL INFORMATION:
(i) APPLICANT: Children's Medical Center Corporaton
(ii) TITLE OF INVENTION: Synducin Mediated Modulation of Tissue Repair
(iii) NUMBER OF SEQUENCES: 4
(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Patrea L. Pabst
(B) STREET: 2800 One Atlantic Center
1201 West Peachtree
(C) CITY: Atlanta
(D) STATE: Georgia
(E) COUNTRY: USA
(F) ZIP: 30309-3450
(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25
(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (404)-873-8794
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(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
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(A) AUTHORS: Lee, Jong-Youn
Boman, Hans G.
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Arg Arg Arg Pro Arg Pro Pro Tyr Leu Pro Arg Pro Arg Pro Pro Pro
1 5 10 15

Phe Phe Pro Pro Arg Leu Pro Pro Arg Ile Pro Pro Gly Phe Pro Pro
20 25 30

Arg Phe Pro Pro Arg Phe Pro [SEQ ID NO:1]
35

Fig. 10